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Exposure to Heavy Charged Particles Affects Thermoregulation in Rats

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Rats exposed to 0.1–5 Gy of heavy particles (^{56}Fe, ^{40}Ar, ^{20}Ne or ^{4}He) showed dose-dependent changes in body temperature. Lower doses of all particles produced hyperthermia, and higher doses of ^{20}Ne and ^{56}Fe produced hypothermia. Of the four HZE particles, ^{56}Fe particles were the most potent and ^{4}He particles were the least potent in producing changes in thermoregulation. The ^{20}Ne and ^{40}Ar particles produced an intermediate level of change in body temperature. Significantly greater hyperthermia was produced by exposure to 1 Gy of ^{20}Ne, ^{40}Ar and ^{56}Fe particles than by exposure to 1 Gy of ^{60}Co γ rays. Pretreating rats with the cyclo-oxygenase inhibitor indomethacin attenuated the hyperthermia produced by exposure to 1 Gy of ^{56}Fe particles, indicating that prostaglandins mediate ^{56}Fe-particle-induced hyperthermia. The hypothermia produced by exposure to 5 Gy of ^{56}Fe particles is mediated by histamine and can be attenuated by treatment with the antihistamines mepyramine and cimetidine.

INTRODUCTION

When manned exploration of the solar system continues, astronauts leaving the protection of the Earth's magnetic field will be exposed to types and doses of radiation significantly different from those in low-Earth orbit, primarily cosmic rays. Cosmic rays are composed of protons, α particles and heavy particles with high charge and energy (HZE). Previous research using a variety of end points has shown that exposure to HZE particles, especially ^{56}Fe ions, can cause deficits in behavioral and neurochemical processes at doses that are significantly lower than those required for similar effects after exposure to γ rays. Protecting the organism against the deleterious effects of exposure to HZE particles requires that we determine the toxicity of these particles across a range of different physiological and behavioral end points, and that we understand the mechanisms by which such exposures can affect these end points (*1–6*).

One of the physiological effects of exposure to ionizing radiation involves alterations in the regulation of body temperature. In rats, γ irradiation produces a dual effect: lower doses (~5 Gy) produce hyperthermia, and higher doses (~50 Gy) produce hypothermia (*7, 8*). This effect results from direct irradiation of the brain because exposures that exclude the brain have no significant effects on the thermoregulatory system (*7, 8*). The dual effects on thermoregulation observed after irradiation with γ rays apparently are mediated by two separate mechanisms. Radiation-induced hyperthermia is mediated by a release of prostaglandins and can be prevented by pretreating rats with indomethacin, which acts to inhibit synthesis of prostaglandins. In contrast, the hypothermia observed after higher doses of radiation is mediated by the release of histamine and can be prevented by treatment with antihistamines (*7, 8*).

Thermoregulation is one of a group of homeostatic processes that mediate the adjustment of an organism to its environment by functioning to maintain a relatively constant internal environment. The observation that exposure to ionizing radiation can disrupt the functioning of this system may be indicative of the potential disruption of a variety of other homeostatic systems. As such, it would be important to establish the sensitivity of homeostatic processes, such as thermoregulation, and the mechanisms that mediate the responses of these systems to HZE particles, to assess the possible effects of such exposures on the performance of astronauts on long-term missions outside the magnetosphere. This is particularly important because, as indicated above, previous research has shown that exposure to heavy particles can disrupt behavioral and physiological functioning at significantly lower doses than exposure to γ rays (*1–6*).

Our experiments were designed to evaluate the effects of exposure to different HZE particles on thermoregulation

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by establishing the dose–response relationships between exposure to iron, argon, neon and helium ions and changes in body temperature. In addition, the roles of prostaglandins and histamine in changes in thermoregulation induced by HZE particles were investigated to determine whether mechanisms that are similar to those that mediate these responses after exposure to γ rays (*7, 8*) also mediate these changes after exposure to heavy particles.

MATERIALS AND METHODS

Experimental animals. Male Sprague-Dawley Crl:CD(SD)BRD rats weighing 200–300 g (Charles River) were used in these experiments. The rats were maintained at Lawrence Berkeley Laboratory (LBL) in AAALAC-accredited facilities. Commercial rodent chow and water were available *ad libitum*. Animal holding rooms were maintained at 21 ± 1°C with a 12-h light:dark cycle.

Radiation and dosimetry. Exposure to heavy particles was performed using the BEVALAC at LBL. Rats were exposed unilaterally to doses of 0.1–5 Gy at dose rates from 0.2 Gy/min to 2 Gy/min. All exposures were in the plateau region of the Bragg curve. Sham-irradiated rats were held in restraining cages for the same of length of time and in the same environment as their irradiated counterparts. Groups of rats were exposed to the following particles (8 rats/particle/dose): iron [^{56}Fe, 600 MeV/*u*, linear energy transfer (LET) = ~190.0 keV/μm]; neon (^{20}Ne, 522 MeV/*u*, LET = ~28.0 keV/μm); argon (^{40}Ar, 670 MeV/*u*, LET = ~85.0 keV/μm); and helium (^{4}He, 165 MeV/*u*, LET = ~2.0 keV/μm).

Dosimetry was provided by the staff of the BEVALAC facility. These procedures have been detailed in previous reports (*5, 9–11*).

Drugs and administration. The drugs tested for effects on changes in thermoregulation induced by HZE particles were indomethacin (Sigma Chemical Co., St. Louis, MO) dissolved in a mixture of 1% sodium hydroxide and sterile nonpyrogenic saline, mepyramine maleate (Mallinckrodt Inc., St. Louis, MO) dissolved in saline, and cimetidine (Smith Kline and French Laboratories, Philadelphia, PA) dissolved in 0.1 ml of 1 N HCl and diluted to the final volume with sterile nonpyrogenic saline. Indomethacin is a cyclo-oxygenase inhibitor which acts to inhibit prostaglandin synthesis. Mepyramine and cimetidine are antihistamines, which are H1 and H2 antagonists, respectively.

Indomethacin was administered by intraperitoneal (ip) injection. Mepyramine and cimetidine were administered using intracerebro-ventricular injection with chronic cannulas placed in the lateral ventricle. Cannulas were implanted stereotaxically in rats anesthetized with an intramuscular injection of 1 ml/kg of a mixture of ketamine (50 mg/kg), xylazine (5 mg/kg) and acepromazine (1 ml/kg). A single cannula was inserted aseptically into the lateral ventricle at 0.8 mm posterior and 2.5 mm lateral to bregma, using coordinates derived from the atlas of Pelligrino *et al.* (*12*). The cannula was lowered until cerebrospinal fluid rose in the cannula. Dental acrylic was used to secure the cannula. The rats were allowed to recover for 2 days before being used for experiments. After the experiment, the rats were sacrificed with CO_2 inhalation, and the injection site was verified histologically.

Procedure. All experiments were performed at an environmental temperature of 21 ± 1°C. The measurement of body temperature was performed as described previously (*7, 8*). Briefly, the animals were placed in acrylic restraining cages 30 min before irradiation, and body temperatures were measured with thermistor probes (YSI series 700, Yellow Springs Instrument Co., Inc., Yellow Springs, OH) inserted approximately 6 cm into the rectum and connected to a datalogger (Minitrend 205). The probes were removed from the animals for irradiation. After exposure, the probes were reinserted, and body temperatures were observed for an additional 30 min. Immediately after radiation exposure, rats developed hyperthermia or hypothermia, depending on the dose, reaching maximum temperature responses in 10 min which lasted for 1 h and then gradually declined.

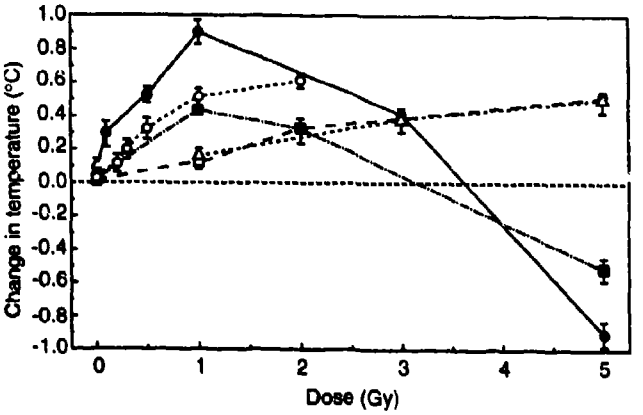

FIG. 1. Average change in rectal temperatures of rats 10 min after exposure to varying doses of (●) ^{56}Fe, (○) ^{40}Ar, (■) ^{20}Ne, (□) ^{4}He and (△) ^{60}Co. Data for ^{60}Co have been regraphed from ref. (*8*). Error bars indicate the standard error of the mean.

For the experiments on the mechanisms of radiation-induced changes in thermoregulation, the appropriate drugs were administered to independent groups of rats (8 rats/group) 30 min before exposure to ^{56}Fe particles. The role of prostaglandins in ^{56}Fe-particle-induced hyperthermia was determined in rats given ip injections of indomethacin and exposed to 1 Gy. The role of histamine in ^{56}Fe-particle-induced hypothermia was determined in rats given either cimetidine or mepyramine injections (intracerebro-ventricular) and exposed to 5 Gy. After exposure, body temperatures were monitored for an additional 30 min. Control animals were administered only the vehicle prior to irradiation. Previous research (*7, 8*) has shown that administration of these drugs alone produces no significant changes in body temperature.

Statistics. Statistical evaluations of the data were performed using analyses of variance. *Post hoc* comparisons between groups were performed using Tukey's *t* test.

RESULTS

The effects of exposure to heavy particles on body temperature are summarized in Fig. 1. Exposing rats to 0.1–5 Gy of ^{56}Fe, ^{40}Ar, ^{20}Ne or ^{4}He particles produced significant dose-dependent changes in body temperature (independent one-way analyses of variance, all $P < 0.001$). Lower doses of all particles produced significant increases in body temperature, while higher doses of ^{56}Fe and ^{20}Ne particles (>3 Gy) caused significant hypothermia.

Figure 1 also shows that the doses needed to produce hyperthermia after exposure were different for the heavy particles. The lowest effective dose for a significant increase in body temperature was observed after exposure to ^{56}Fe particles (~0.1 Gy), while the highest effective dose was observed after exposure to ^{4}He particles (~0.5 Gy). The intermediate effective dose for a significant increase in temperature was observed after exposure to 0.3 Gy of ^{20}Ne or 0.2

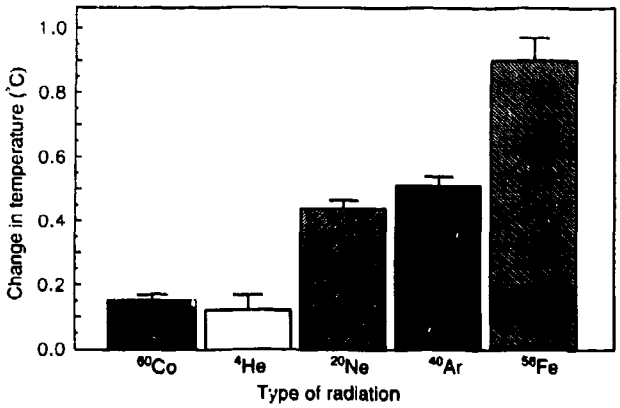

FIG. 2. Comparison of the hyperthermia produced by exposure to 1 Gy of ^{60}Co γ rays with that produced by exposure to 1 Gy of heavy particles. Data for ^{60}Co have been regraphed from ref. (*8*). Error bars indicate the standard error.

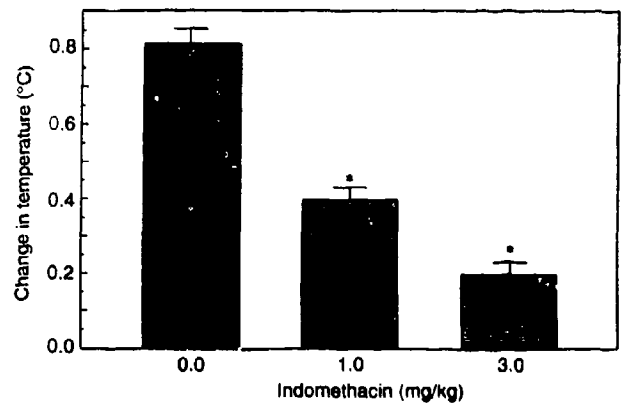

FIG. 3. Effect of indomethacin (1.0 or 3.0 mg/kg) on hyperthermia induced by exposure to 1 Gy of ^{56}Fe particles. Significantly different from ^{56}Fe-particle-induced hypothermia, $P < 0.05$. Error bars indicate the standard error.

Gy of ^{40}Ar particles. Differences were also observed in the hypothermia induced by exposure to different particles. Compared to nonirradiated controls, rats exposed to either ^{56}Fe or ^{20}Ne particles showed a significant reduction in body temperature [$t(14) = 12.52$, $P < 0.01$; $t(14) = 10.67$, $P < 0.01$, respectively] at the highest dose (5 Gy). In contrast, the rats exposed to 5 Gy of ^{4}He particles continued to show a significant increase in body temperature [$t(14) = 8.16$, $P < 0.01$].

The amount of change in body temperature produced by exposure to 1 Gy of heavy particles or to 1 Gy of ^{60}Co γ rays is shown in Fig. 2. This dose was selected because it was common to all of the types of radiation tested. Compared to 1 Gy ^{60}Co γ rays (*7*, *8*), exposure to ^{4}He particles produced an equivalent increase in body temperature [$t(14) < 0.42$, $P > 0.05$]. In contrast, exposure to ^{20}Ne, ^{40}Ar or ^{56}Fe particles produced a significantly greater rise in body temperature than did exposure to ^{60}Co or ^{4}He (all $P < 0.01$). In addition, the hyperthermia produced by ^{56}Fe was significantly greater than that produced by exposure to either ^{20}Ne [$t(14) = 7.72$, $P < 0.01$] or ^{40}Ar [$t(14) = 6.47$, $P < 0.01$], which did not differ significantly from each other [$t(14) = 1.25$, $P > 0.05$].

The dose rate for HZE varied by a factor of 10. For ^{60}Co, the dose rate is 10–20 Gy/min. Because the data for ^{60}Co have been regraphed from ref. (*8*), the dose rates were not included in this paper. Research using low-LET radiation in the Armed Forces Radiobiology Research Institute has indicated that there is no significant change in temperature responses with dose rates between 10–20 Gy per minute.

The effect of pretreatment with indomethacin on ^{56}Fe-particle-induced hyperthermia is shown in Fig. 3. Compared to irradiated rats given only the vehicle, both doses of indomethacin (1 or 3 mg/kg, ip) produced a significant attenuation of the hyperthermia induced by a 1-Gy dose of ^{56}Fe particles [$t(14) = 7.90$, $P < 0.01$; $t(14) = 11.74$, $P < 0.01$, respectively]. Similarly, the 3-mg/kg dose of indomethacin produced a significantly greater attenuation of ^{56}Fe-particle-induced hyperthermia than did the 1-mg/kg dose [$t(14) = 3.83$, $P < 0.01$].

Compared to the vehicle-treated rats (Fig. 4), both mepyramine and cimetidine (100 and 300 mg) produced significant dose-dependent attenuations of the hypothermia produced by exposure to 5 Gy ^{56}Fe particles (all $P < 0.01$). The degree of attenuation of the ^{56}Fe-particle-induced hypothermia was greater for the higher doses of both the mepyramine-treated [$t(14) = 4.80$, $P < 0.01$] and the cimetidine-treated [$t(14) = 4.60$, $P < 0.01$] rats. The differences between the effectiveness of ^{56}Fe-particle-induced hypothermia attenuated by mepyramine and cimetidine were not statistically significant (all $P > 0.05$).

DISCUSSION

The present results show that exposure to heavy particles produces significant dose-dependent changes in body temperature in rats. As observed after exposure to γ rays (*7*, *8*), lower doses of HZE particles induce hyperthermia, whereas higher doses of ^{20}Ne and ^{56}Fe particles induce hypothermia.

The ^{56}Fe particles were the most effective in producing changes in thermoregulation. Exposure to ^{56}Fe particles produced significant hyperthermia at the lowest dose and also produced the greatest amount of change in body temperature at any given dose. Exposing rats to ^{60}Co γ rays produces a significant increase in body temperature at a dose of 5 Gy, whereas a dose of 50 Gy is needed to produce

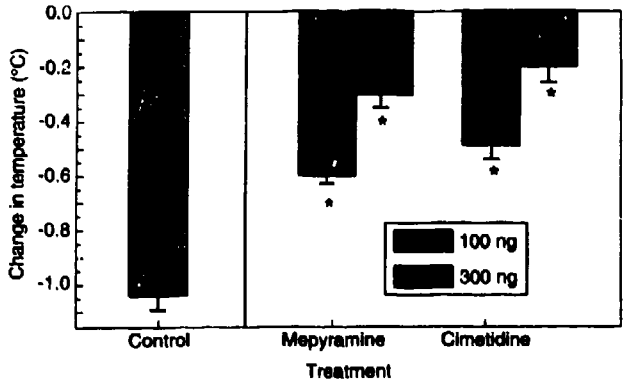

FIG. 4. Effect of mepyramine and cimetidine (100 and 300 ng, intracerebro-ventricular injection) on hypothermia induced by exposure to 5 Gy of ^{56}Fe particles. Control animals received vehicle only. *Significantly different from ^{56}Fe-particle-induced hypothermia, $P < 0.05$. Error bars indicate the standard error.

a significant decrease in body temperature (*7, 8*). In contrast, significant increases in body temperature are obtained after exposure to 0.1 Gy of ^{56}Fe particles and significant decreases are obtained with 5 Gy.

This observation extends the results of previous studies using a variety of different neurochemical and behavioral end points to the maintenance of physiological homeostasis. In agreement with the results of previous research that used conditioned taste aversion (*2, 4*) and striatal dopamine release (*1, 3, 5*) in rats and emesis in ferrets (*6*), the present results show that ^{56}Fe particles produce changes in thermoregulation at significantly lower doses than the other particles tested.

Although exposure to ^{56}Fe particles is significantly more effective in producing changes in thermoregulation than exposure to ^{20}Ne or ^{40}Ar particles, these latter particles are nevertheless significantly more effective than ^{4}He particles or ^{60}Co. These results indicate that, for this particular end point, the effectiveness of exposure to these particles in producing changes in thermoregulation generally parallels the LET of the particles. The most effective particle, ^{56}Fe, was the one with the highest LET (~190 keV/μm), while the particle with the lowest LET, ^{4}He (~2 keV μm), did not differ from ^{60}Co γ rays (LET, 0.3 keV/μm) in effectiveness. The two particles with intermediate LETs, ^{20}Ne (~28 keV/μm) and ^{40}Ar (~85 keV/μm), showed an intermediate level of effectiveness in eliciting changes in thermoregulation compared to ^{60}Co and ^{56}Fe. However, there were no differences in the changes in thermoregulation produced by ^{20}Ne and ^{40}Ar in rats exposed to the common dose of 1 Gy, despite the differences in particle LET.

In terms of the relationship between LET and the amount of change behavior and neurochemistry produced by exposure to different types of radiation, the present results differ from those obtained using the conditioned taste aversion (*2, 4*) or striatal dopamine release (Joseph, Rabin, Hunt and Kandasamy, unpublished observations) as experimental end points. In those experiments, ^{60}Co γ rays and ^{4}He, ^{20}Ne and ^{40}Ar ions were equally effective in producing changes in behavior and neurochemistry. With these end points, only ^{56}Fe particles were significantly more effective than γ rays. These results therefore emphasize the importance of the specific end point in determining the effectiveness of heavy particles (*1, 2, 4, 9, 13–15*).

As observed previously after exposure to ^{60}Co γ rays (*7, 8*), separate mechanisms mediate hyperthermia and hypothermia after exposure to ^{56}Fe particles. Hyperthermia produced by exposure to 1 Gy of ^{56}Fe particles is mediated by α particle-induced release of prostaglandins because pretreatment with the cyclo-oxygenase inhibitor indomethacin, which inhibits prostaglandin synthesis, causes a significant reduction in the ^{56}Fe-particle-induced increase in body temperature. Hypothermia produced by exposure to 5 Gy of ^{56}Fe particles is mediated by the release of histamine and can be prevented by pretreatment with either H1 (mepyramine) or H2 (cimetidine) antagonists. Because these compounds have identical effects on changes in thermoregulation produced by exposure to γ rays and HZE particles, similar mechanisms must mediate the thermoregulatory responses after exposure to these different types of radiation. This observation, that similar mechanisms mediate the response of the organism both to γ rays and to ^{56}Fe particles, is in agreement with the report that lesions of the area postrema are equally effective in disrupting the acquisition of a conditioned taste aversion produced by exposure to both types of radiation (*2*). Thus the present results would be consistent with the hypothesis that the differences between ^{60}Co γ rays and ^{56}Fe particles seem to be differences in the potency with which these types of radiation effect changes, either directly or indirectly, in the functioning of the nervous system.

In summary, the present results show that exposure to HZE particles produces changes in the regulation of body temperature at doses that are significantly lower than those needed after exposure to γ rays. These results therefore extend previous research which used a variety of other neurochemical and behavioral end points (*1–6*) to the maintenance of physiological homeostasis. Homeostatic mechanisms, including regulation of body temperature, salt balance, glucose metabolism, etc., function to maintain a relatively constant internal environment despite wide variations in the external environment. The observation that exposure to relatively low doses of heavy charged particles (specifically, ^{20}Ne, ^{40}Ar and ^{56}Fe) can disrupt the homeostatic regulation of body temperature suggests that other homeostatic systems may be sensitive to low doses of HZE particles.

Because changes in thermoregulation produced by ionizing radiation are mediated by the brain (7), these results suggest the possibility that the cumulative effects of exposure to HZE particles on long-term space missions beyond the Earth's magnetosphere could result in a disturbance of homeostatic processes that could in turn affect the performance capabilities of astronauts. However, because the fluences of HZE particles are low and because the sensitivity of humans to these particles is unknown, additional research will be necessary, at some point, to evaluate this possibility.

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